NEW DRUG APPROVALS

Tecovirimat for Smallpox

The FDA has approved an antiviral pill, tecovirimat (Tpoxx, Siga Technologies), as the first drug intended to treat smallpox. Tecovirimat has never been tested in humans with smallpox because the disease was declared eradicated in 1980, three years after the last known case.

The approval could halt a lethal pandemic if the virus were to be released as a terrorist bioweapon or through a laboratory accident.

The drug was very effective at protecting animals deliberately infected with monkeypox and rabbitpox, two related diseases that can be lethal. It also caused no severe side effects when safety-tested in 359 healthy human volunteers, the FDA said.

Research on tecovirimat—originally designated ST-246—began after the 9/11 terrorist attack on the World Trade Center. The research accompanied efforts to stretch the national stockpile of smallpox vaccine by safely diluting it.

Although circulating smallpox has been eradicated, two known stores of the virus exist in laboratory freezers—one in Russia and one at the Centers for Disease Control and Prevention in Atlanta.

Bioterrorism experts fear that other stockpiles may exist; for example, in 2014 several forgotten vials containing smallpox were found at the National Institutes of Health.

Sources: FDA, *The New York Times*, July 13, 2018

Braftovi, Mektovi for Melanoma

The FDA has approved encorafenib and binimetinib (Braftovi and Mektovi, Array BioPharma Inc.) in combination for patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, as detected by an FDA-approved test.

Approval was based on a randomized, active-controlled, open-label, multicenter trial in 577 patients with *BRAF* V600E or V600K mutation-positive unresectable or metastatic melanoma. The most common adverse reactions in patients receiving the combination were fatigue, nausea, diarrhea, vomiting, abdominal pain, and arthralgia. Discontinuation of therapy due to adverse reactions occurred in 5% of patients receiving the combination; the most common reasons were hemorrhage and headache.

The FDA also approved the THxID BRAF Kit (bioMérieux) as a companion diagnostic for these therapeutics.

Source: FDA, June 27, 2018

Zemdri for UTIs

Plazomicin (Zemdri, Achaogen, Inc.) has received FDA approval for the treatment of adults with complicated urinary tract infections (cUTIs), including pyelonephritis, caused by certain *Enterobacteriaceae* in patients who have limited or no alternative treatment options. Plazomicin is an intravenous infusion, administered once daily, that is designed to retain potent activity in the face of certain difficult-to-treat multidrug-resistant infections.

The approval of plazomicin is supported by data from the phase 3 EPIC clinical trial. The most common side effects were decreased kidney function, diarrhea, hypertension, headache, nausea, vomiting, and hypotension.

Regarding a potential indication for plazomicin for the treatment of bloodstream infection, the FDA issued a complete response letter stating that the CARE study does not provide substantial evidence of effectiveness of plazomicin for this treatment. The company intends to meet with the FDA to determine whether there is a feasible resolution.

Source: Achaogen, June 26, 2018

Epidiolex for Rare Epilepsy

The FDA has approved GW Research Ltd.'s Epidiolex (cannabidiol [CBD]) oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy—Lennox–Gastaut syndrome and Dravet syndrome—in patients 2 years of age and older. This is the first FDA-approved drug that contains a purified substance derived from marijuana. Children with Dravet syndrome typically experience poor development of language and motor skills, hyperactivity, and difficulty relating to others.

CBD, a chemical component of the *Cannabis sativa* plant, does not cause the intoxication or euphoria that comes from tetrahydrocannabinol (THC), the primary psychoactive component of marijuana.

Epidiolex's effectiveness was studied in three randomized, double-blind, placebo-controlled clinical trials involving 516 patients with one of the two syndromes. Epidiolex, taken with other medications, was effective in reducing the frequency of seizures compared with placebo.

The most common side effects in Epidiolex-treated patients were sleepiness, sedation, and lethargy; elevated liver enzymes; decreased appetite; diarrhea; rash; fatigue, malaise, and weakness; insomnia, sleep disorders and poor-quality sleep; and infections.

Epidiolex must be dispensed with a patient medication guide. The most serious risks include thoughts about suicide, attempts to commit suicide, feelings of agitation, new or worsening depression, aggression, and panic attacks. Epidiolex also caused liver injury, generally mild, but raising the possibility of rare but more severe injury.

CBD is a Schedule I controlled substance, and the company conducted nonclinical and clinical studies to assess the abuse potential of CBD.

Source: FDA, June 25, 2018

Generic Approvals

Fulphila, a Neulasta Biosimilar

The FDA has approved Fulphila (pegfilgrastim-jmdb, Mylan GmbH) as the first biosimilar to Amgen's Neulasta (pegfilgrastim) to decrease the chance of infection as suggested by febrile neutropenia in patients with nonmyeloid cancer who are receiving myelosuppressive chemotherapy that has a clinically significant incidence of febrile neutropenia.

Fulphila was approved as a biosimilar, not as an interchangeable product.

The most common side effects of Fulphila are bone pain and pain in extremities. Patients with a history of serious allergic reactions to human granulocyte colony-stimulating factors, such as pegfilgrastim or filgrastim products, should not take Fulphila. Serious side effects from treatment with Fulphila include rupture of the spleen, acute respiratory distress syndrome, serious allergic reactions including anaphylaxis, glomerulonephritis, leukocytosis, capillary leak syndrome, and the potential for tumor growth. Fatal sickle cell crises have occurred.

Source: FDA, June 4, 2018

Suboxone Sublingual Film

The FDA has approved the first generic versions of buprenorphine/naloxone sublingual film (Suboxone, Indivior PLC) for the treatment of opioid dependence.

Mylan Technologies, Inc., and Dr. Reddy's Laboratories SA received FDA approval to market buprenorphine and naloxone sublingual film in multiple strengths. However, patent disputes may affect the product launches.

Adverse events commonly observed with the buprenorphine/naloxone sublingual film are oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. These products may only be prescribed by Drug Addiction Treatment Act–certified prescribers.

Sources: FDA, June 14, 2018; and Indivior, June 15, 2018

NEW INDICATIONS

Opdivo, Yervoy Combination For Colorectal Cancer Cases

The combination of nivolumab (Opdivo) and ipilimumab (Yervoy), both made by Bristol-Myers Squibb, has received FDA accelerated approval for the treatment of adult and pediatric patients 12 years of age and older with microsatellite instability high or mismatch repair deficient metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The approval was based on data from this population in CheckMate-142, an ongoing phase 2, multicenter, nonrandomized, multiple-parallel cohort, open-label study. Among the 82 patients, 46% responded to treatment with nivolumab plus ipilimumab (3.7% complete responses and 43% partial responses). Among these 38 responders, the median duration of response was not reached.

The recommended dosing schedule is nivolumab 3 mg/kg, followed by ipilimumab 1 mg/kg on the same day, every three weeks for four doses, followed by nivolumab maintenance therapy (240 mg every two weeks) after completion of four doses of the combination until disease progression or unacceptable toxicity. All doses are administered as intravenous infusions over 30 minutes.

In the nivolumab plus ipilimumab cohort of CheckMate-142, nivolumab was discontinued in 13% of patients and delayed in 45% of patients due to an adverse reaction. Serious adverse reactions occurred in 47% of patients. The most frequent serious adverse reactions were colitis/diarrhea, hepatic events, abdominal pain, acute kidney injury, pyrexia, and dehydration. The most common adverse reactions were fatigue, diarrhea, pyrexia, musculoskeletal pain, abdominal pain, pruritus, nausea, rash, decreased appetite, and vomiting. Ipilimumab carries a boxed warning for the possibility of severe and fatal immune-mediated adverse reactions.

Source: Bristol-Myers Squibb, July 11, 2018

Keytruda for PMBCL...

The FDA has approved pembrolizumab (Keytruda, Merck) for the treatment of adult and pediatric patients who have refractory primary mediastinal large B-cell lymphoma (PMBCL) or who have relapsed after two or more prior lines of therapy. The indication received FDA accelerated approval based on tumor response rate and durability of response. Pembrolizumab is not recommended for the treatment of patients with PMBCL who require urgent cytoreductive therapy.

Pembrolizumab is the first anti–programmed death-1 therapy approved for the treatment of PMBCL, a type of non-Hodgkin's lymphoma.

The approval was based on data from KEYNOTE-170, a multicenter, open-label, single-arm trial evaluating pembrolizumab in 53 patients with relapsed or refractory PMBCL. Patients received pembrolizumab 200 mg every three weeks until unacceptable toxicity or documented disease progression, or for up to 24 months for patients who did not progress.

The overall response rate was 45%, with a complete response rate of 11% and a partial response rate of 34%. Based on 24 patients who responded, median duration of response was not reached and the median time to first objective response was 2.8 months. Median follow-up time was 9.7 months.

Pembrolizumab was discontinued due

to adverse reactions in 8% of patients, and treatment was interrupted due to adverse reactions in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 26% of patients, including arrhythmia, cardiac tamponade, myocardial infarction, pericardial effusion, and pericarditis. Six patients died within 30 days of starting treatment. The most common adverse reactions were musculoskeletal pain, upper respiratory tract infection, pyrexia, cough, fatigue, and dyspnea.

Experience is limited with pembrolizumab in pediatric patients. Efficacy for pediatric patients with PMBCL was extrapolated from the results in the adult PMBCL population.

Source: Merck, June 13, 2018

...and for Cervical Cancer

Pembrolizumab has also received FDA approval for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express programmed death ligand-1 (PD-L1) as determined by an FDA-approved test.

Pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer in a single cohort of KEYNOTE 158, a multicenter, nonrandomized, open-label, multicohort trial. Patients were treated with pembrolizumab 200 mg intravenously every three weeks until unacceptable toxicity or documented disease progression. This new approval was based on 77 patients who had tumors that expressed PD-L1 and who had received at least one line of chemotherapy for metastatic disease. With a median follow-up of 11.7 months, the objective response rate in these patients was 14.3% (2.6% complete responses and 11.7% partial responses). No responses were observed in patients whose tumors did not express PD-L1.

The most common adverse reactions were fatigue, pain, pyrexia, peripheral edema, musculoskeletal pain, diarrhea/colitis, abdominal pain, nausea, vomiting, constipation, decreased appetite, hemorrhage, urinary tract infections (UTIs), infections, rash, hypothyroidism, headache, and dyspnea. Pembrolizumab was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients. The most frequent serious adverse reactions included anemia, fistula, hemorrhage, and infections (except UTIs).

The FDA concurrently approved PD-L1 IHC 22C3 pharmDx (Dako North America Inc.) as a companion diagnostic.

Source: FDA, June 12, 2018

Bevacizumab for Ovarian Cancer

The FDA has approved bevacizumab (Avastin, Genentech) for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by single-agent bevacizumab, for stage III or IV disease after initial surgical resection.

Approval was based on GOG-0218, a multicenter, randomized, double-blind, placebo-controlled, three-arm study. Median progression-free survival (PFS) was 18.2 months for patients receiving bevacizumab with chemotherapy followed by single-agent bevacizumab; 12.8 months for those receiving bevacizumab with chemotherapy without single-agent bevacizumab; and 12.0 months for those receiving chemotherapy without bevacizumab. Estimated median overall survival was 43.8 months with bevacizumab and chemotherapy followed by bevacizumab compared with 40.6 months with chemotherapy alone.

Adverse reactions occurring at a higher incidence with bevacizumab were diarrhea, nausea, stomatitis, fatigue, arthralgia, muscular weakness, pain in extremity, dysarthria, headache, dyspnea, epistaxis, nasal mucosal disorder, and hypertension. Serious adverse reactions were fatigue, hypertension, and decreased platelet and white blood cell counts.

Source: FDA, June 13, 2018

Venclexta for CLL, SLL

The FDA has approved venetoclax (Venclexta, AbbVie Inc./Genentech Inc.) for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.

Approval was based on MURANO, a randomized, multicenter, open-label trial of venetoclax with rituximab (VEN/R) versus bendamustine with rituximab (B/R) in 389 patients with CLL who had received at least one prior line of therapy. After a median follow-up of 23 months, the median progression-free survival was not reached in the VEN/R arm and was 18.1 months in the B/R arm. The overall response rate was 92% in the VEN/R arm compared to 72% for those treated with B/R.

In patients treated with VEN/R, the most common adverse reactions were neutropenia, diarrhea, upper respiratory tract infection, fatigue, cough, and nausea. Grade 3 or 4 neutropenia developed in 64% of these patients, and grade 4 neutropenia developed in 31%. Serious adverse reactions occurred in 46% of patients. Serious infections developed in 21% of patients, most commonly pneumonia (9%). Due to rapid reduction in tumor volume, tumor lysis syndrome is an important identified risk with venetoclax treatment.

Source: FDA, June 8, 2018

Moxidectin for River Blindness

The FDA has approved 8 mg oral

moxidectin (Medicines Development for Global Health [MDGH]) for the treatment of river blindness (onchocerciasis) in patients 12 years of age and older. The FDA has also awarded MDGH a priority review voucher.

River blindness is caused by a parasitic worm, *Onchocerca volvulus*. The disease manifests as severe itching, disfiguring skin conditions, and visual impairment, including permanent blindness, caused by the worm's larvae (microfilariae).

The approval of moxidectin was based on data from two randomized, double-blind, active-controlled clinical studies. Each study met its respective primary endpoints, showing a statistically significant superiority of moxidectin over the current standard of care, ivermectin, in suppressing the presence of the microfilariae in skin. Results from the phase 3 study were published in the *Lancet* in January 2018.

The World Health Organization Special Program for Research and Training in Tropical Diseases was instrumental in the development of moxidectin.

Source: MDGH, June 13, 2018

FDA REVIEW ACTIVITIES

Breakthrough Therapy Status

HTX-011 for Pain

HTX-011 (Heron Therapeutics) has received a breakthrough therapy designation. HTX-011 is an investigational, long-acting, extended-release formulation of the local anesthetic bupivacaine in a fixed-dose combination with the anti-inflammatory meloxicam for the management of postoperative pain.

The designation was granted based on results of phase 2 and 3 studies that showed HTX-011 significantly reduced both pain intensity and the need for opioids through 72 hours post-surgery, compared with placebo and bupivacaine solution, the standard of care.

HTX-011 has been shown to reduce pain significantly better than placebo or bupivacaine alone in five diverse surgical models: hernia repair, abdominoplasty, bunionectomy, total knee arthroplasty, and breast augmentation. By delivering sustained levels of both a potent anesthetic and a local anti-inflammatory agent directly to the site of tissue injury, HTX-011 also reduces the need for systemically administered pain medications such as opioids.

Source: Heron Therapeutics, June 21, 2018

Fast-Track Designations

Mirvetuximab Soravtansine for Platinum-Resistant Ovarian Cancer

The FDA has granted a fast-track designation to ImmunoGen for mirvetuximab soravtansine, an antibody-drug conjugate (ADC). It is intended for patients with medium-to-high folate receptor alpha (FRα)-positive platinum-resistant ovarian cancer who have been on one to three prior systemic regimens, and for whom single-agent chemotherapy is appropriate.

Approximately 19,000 women in the U.S. have platinum-resistant ovarian cancer requiring second-line or later treatment. ImmunoGen estimates that 60% of ovarian cancer cases have medium or high FRα expression.

Mirvetuximab soravtansine is being studied in two comparison trials: a phase 3 trial comparing it with single-agent chemotherapy, and a phase 1b/2 study with bevacizumab (Avastin, Genentech), pembrolizumab (Keytruda, Merck), and a triplet combination of mirvetuximab plus carboplatin and bevacizumab.

Source: ImmunoGen, June 18, 2018

Raviten for Intradialytic Hypotension

TrioxBio Inc. has received fast-track designation for Raviten (MTR-107), an injectable solution of S-ethylisothiouronium diethylphosphate. Raviten is intended for patients with end-stage renal disease who are undergoing hemodialysis and are at risk for intradialytic hypotension, a common complication of hemodialysis associated with increased morbidity and mortality.

The drug has been shown in preclinical and exploratory clinical trials to inhibit inducible nitric oxide synthase (NOS), endothelial NOS, and neuronal NOS, thereby controlling overproduction of nitric oxide. It also normalizes low blood pressure in patients suffering from intradialytic hypotension, as well as other low blood pressure conditions.

TrioxBio is planning phase 2 clinical trials for late 2018.

Source: TrioxBio, May 29, 2018

RGX-111 for Mucopolysaccharidosis Type I

REGENXBIO Inc. has been granted fast-track designation for RGX-111, a novel, one-time investigational treatment for mucopolysaccharidosis type I (MPS I).

MPS I is a rare autosomal recessive genetic disease caused by the deficiency of an enzyme required for the breakdown of glycosaminoglycans (GAGs) in lysosomes. GAGs accumulate in tissues of MPS I patients, resulting in characteristic storage lesions and diverse clinical signs and symptoms, including spinal cord compression and cognitive impairment.

RGX-111 delivers the human iduronidase (*IDUA*) gene directly to the central nervous system. This could provide a permanent source of secreted IDUA, which is otherwise untreated in intravenous-only therapy due to the blood–brain barrier, allowing for long-term cross-correction of cells throughout the central nervous system. This strategy could also potentially prevent the progression of cognitive deficits.

RGX-111 will be evaluated in a phase 1, multicenter, open-label study in chil-

dren and adults with MPS I. Patients will receive immunosuppression for the first year after RGX-111 is administered. The primary purpose of the clinical study is to assess the safety and tolerability of RGX-111 at 24 weeks. The study will also assess biomarkers related to IDUA protein activity within the cerebrospinal fluid, serum, and urine. Following completion of the primary study period, subjects will continue to be assessed for 104 weeks.

Source: REGENXBIO Inc., June 12, 2018

Betalutin for Follicular Lymphoma

Nordic Nanovector has received fast-track designation for Betalutin (177Lu-lilotomab satetraxetan) for the treatment of patients with relapsed or refractory follicular lymphoma after at least two prior systemic therapies.

The designation is based on the promising safety and preliminary efficacy data in patients with relapsed/refractory indolent non-Hodgkin's lymphoma from the first part of the LYMRIT 37-01 study. Currently, the PARADIGME trial is focusing on third-line CD20-refractory follicular lymphoma patients, comparing two dosing regimens. An initial efficacy and safety data read-out for PARADIGME is targeted for the first half of 2020.

Source: Nordic Nanovector, June 12, 2018

Fimepinostat for Diffuse Large B-Cell Lymphoma

The FDA has granted a fast-track designation to Curis for fimepinostat (formerly CUDC-907) in adults with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL) after two or more lines of systemic therapy.

Phase 1 and phase 2 clinical studies demonstrated that treatment with fimepinostat resulted in a complete or partial response in approximately one out of every four patients with R/R DLBCL with *MYC* alterations. The median duration of response for all responding patients in these studies was more than one year.

Source: Curis, May 31, 2018

Priority Review Status

Hemlibra for Hemophilia A

The FDA has accepted Genentech's supplemental biologics license application and granted priority review for emicizumab-kxwh (Hemlibra) for adults and children with hemophilia A with factor VIII inhibitors. The FDA is expected to make a decision by October 4, 2018.

Emicizumab is designed to bring together factors IXa and X, proteins required to activate the natural coagulation cascade and restore the blood-clotting process for hemophilia A patients. Emicizumab is a prophylactic treatment administered as a once-weekly subcutaneous injection.

The application is based on data from the phase 3 HAVEN 3 study, in which patients who received emicizumab every week or every two weeks showed a 96% to 97% reduction in treated bleeds, compared with those who received no prophylaxis. In an additional arm of the study, people who had previously received factor VIII prophylaxis in a noninterventional study switched to emicizumab prophylaxis, allowing for an intrapatient comparison of two prophylaxis regimens. In that comparison, emicizumab demonstrated a statistically significant reduction of 68% in treated bleeds, making it the first medicine to show superior efficacy to prior treatment with factor VIII prophylaxis, the standard of care.

Source: Genentech, June 5, 2018

Fycompa CIII for Seizures

The FDA has accepted Eisai's supplemental new drug application for priority review for perampanel (Fycompa) CIII for monotherapy and adjunctive use to treat partial-onset seizures with or without secondarily generalized seizures in patients 2 to 11 years of age. The submission also proposes a pediatric indication for adjunctive use for primary generalized tonic-clonic seizures in pediatric patients with epilepsy. The application includes both the perampanel tablet and oral suspension formulations.

Perampanel is a selective, noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist. The precise mechanism by which perampanel exerts its antiepileptic effects in humans is unknown.

Of the estimated 470,000 children living with epilepsy in the U.S., approximately 30% have uncontrolled seizures. Moreover, about 71% of people living with epilepsy miss at least one dose of medication per month, and 45% of those missed doses result in a subsequent breakthrough seizure. Perampanel has a long half-life of 105 hours, with steady state reached in about two to three weeks. Because of the long half-life, a missed dose does not significantly impact plasma levels, a key risk factor for breakthrough seizures.

The application includes data from two studies evaluating perampanel oral suspension in children with inadequately controlled seizures and children with epilepsy.

Source: Eisai Inc., May 30, 2018

Promacta for Severe Aplastic Anemia

The FDA has granted priority review to eltrombopag (Promacta, Novartis), an oral thrombopoietin receptor agonist, in combination with standard immunosuppressive therapy (IST) for first-line treatment of severe aplastic anemia (SAA).

Eltrombopag is already approved for patients with SAA who have had an insufficient response to standard IST. It is also approved for patients with chronic immune thrombocytopenia who are refractory to other treatments and for

the treatment of thrombocytopenia in patients with chronic hepatitis C virus infection.

The designation is based on Novartis's analysis of research sponsored by the National Heart, Lung, and Blood Institute in which 52% of treatment-naïve SAA patients achieved complete response at six months when treated with eltrombopag concurrently with standard IST, an increase of 35% compared with those treated with standard IST alone. The overall response rate was 85% at six months.

Source: Novartis, May 30, 2018

Larotrectinib for Solid Tumors

Bayer and Loxo Oncology, Inc., have been granted priority review for larotrectinib for the treatment of adults and children with locally advanced or metastatic solid tumors harboring a neurotrophic tyrosine receptor kinase *(NTRK)* gene fusion.

TRK fusion cancer occurs when an *NTRK* gene fuses with an unrelated gene, producing an altered tropomyosin receptor kinase (TRK) protein. The altered TRK fusion protein triggers a signal cascade. These proteins become the primary oncogenic driver of the spread and growth of tumors. *NTRK* gene fusion has been identified in adult and pediatric solid tumors with varying frequencies. Larotrectinib is a TRK inhibitor.

The FDA has set a target action date of November 26, 2018.

Source: Bayer and Loxo Oncology, May 29, 2018

Brexanolone for Postpartum Depression

The FDA has accepted Sage Therapeutics' filing of a new drug application and granted priority review for brexanolone (SAGE-547) for the treatment of postpartum depression (PPD). The FDA assigned a Prescription Drug User Fee Act target date of December 19, 2018. If approved, intravenous brexanolone would be the first medication indicated for the treatment of PPD.

Brexanolone is an allosteric modulator of synaptic and extrasynaptic $GABA_A$ receptors. Allosteric modulation of neurotransmitter receptor activity results in varying degrees of desired activity rather than complete activation or inhibition of the receptor.

Source: Sage Therapeutics, May 30, 2018

Orphan Drug Designations

PCS499 for Necrobiosis Lipoidica

Processa Pharmaceuticals, Inc., has been granted an orphan drug designation for PCS499 for the treatment of necrobiosis lipoidica (NL).

In the U.S., approximately 74,000 to 185,000 people have NL, a multifaceted disorder affecting the skin and the tissue under the skin. There is no FDA-approved treatment. PCS499 will be the first treatment targeted to this condition.

Processa plans to begin clinical studies this year.

Source: Processa Pharmaceuticals, June 22, 2018

AMO-04 for Rett Syndrome

AMO Pharma Ltd. has been granted an orphan drug designation for AMO-04 for the treatment of Rett syndrome, a pediatric neurological disorder first recognized in the 1950s and 1960s.

Typically diagnosed in infancy—almost always in girls—Rett syndrome is a severe genetic disorder caused, in most cases, by mutations in the X-linked methyl-CpG-binding protein 2 (*MECP2*) gene, which was discovered in 1999. The syndrome is thought to be fatal in boys, who lack the extra X chromosome that protects patients from being completely overcome by the disorder. Boys with the cell mutation that causes Rett syndrome often die before or shortly after birth.

Rett syndrome is often misdiagnosed as autism, cerebral palsy, or nonspecific developmental delay because patients usually have problems with cognitive, sensory, emotional, motor, and autonomic function. Other signs and symptoms include seizures, disorganized breathing patterns while awake, scoliosis, abnormal hand movements (including hand wringing) and sleep disturbances.

AMO-04 is a glutamate modulator that has shown early promise in the treatment of Rett syndrome based on screening by the Scout Program, a drug discovery screen in a mouse model of the disease that is sponsored by Rettsyndrome.org. Research conducted by Numedicus, a private biopharmaceutical company focused on the repurposing of drugs, also indicated that AMO-04 could benefit patients living with some breathing disorders.

Sources: AMO Pharma Ltd., June 13, 2018; Rettsyndrome.org

Olinciguat for Sickle Cell Disease

The FDA has granted orphan drug status to Ironwood Pharmaceuticals for olinciguat (IW-1701), a treatment for patients with sickle cell disease.

Patients with sickle cell disease can experience complications including pain crises, chronic pain, acute chest syndrome, pulmonary hypertension, ankle ulcers, renal complications, and serious infections. They're also at risk for strokes and pulmonary complications.

Sickled red blood cells are more susceptible to rupturing, which depletes nitric oxide due to arginase release and hemoglobin scavenging. Olinciguat, an oral soluble guanylate cyclase stimulator, has been shown in nonclinical studies to modulate the nitric oxide/soluble guanylate cyclase/cyclic guanosine monophosphate signaling pathway.

Ironwood is enrolling patients in STRONG-SCD, a multicenter phase 2 trial evaluating olinciguat for the potential

treatment of sickle cell disease.

Source: Ironwood Pharmaceuticals, June 7, 2018

ALN-TTRsc02 for Amyloidosis

Alnylam Pharmaceuticals has been granted an orphan drug designation for ALN-TTRsc02, an investigational RNA interference therapeutic for transthyretin (TTR)-mediated amyloidosis.

TTR-mediated amyloidosis is a progressively debilitating and often fatal disease caused by misfolded TTR proteins that accumulate as amyloid deposits in multiple tissues including the nerves, heart, and gastrointestinal tract. Hereditary ATTR (hATTR) amyloidosis occurs when mutations in the TTR gene cause abnormal amyloid proteins to accumulate and damage body organs and tissues, resulting in intractable peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy, as well as other disease manifestations.

ALN-TTRsc02 is designed to target and silence specific messenger RNA, potentially blocking the production of wild-type and mutant TTR protein. This may reduce the deposition and facilitate the clearance of TTR amyloid deposits in peripheral tissues and potentially restore function to these tissues.

Source: Alnylam Pharmaceuticals, June 4, 2018

GBC0905 for Facioscapulohumeral MD

The FDA has granted orphan drug status to Genea Biocells for GBC0905 for the potentially curative treatment of facioscapulohumeral muscular dystrophy (FSHD).

FSHD is an inheritable disease that consumes skeletal muscle. Aberrant DUX4 expression is the underlying cause of the disease and results in muscle fiber death. GBC0905 blocks the activation of DUX4 target genes and protects affected skeletal muscle cells in a dose-dependent fashion without affecting normal myogenesis.

Source: Genea Biocells, May 31, 2018

PU-H71 for Myelofibrosis

The FDA has granted an orphan drug designation to PU-H71 (Samus Therapeutics) for the treatment of myelofibrosis.

Under conditions of abnormal stress, cells become biochemically "rewired" to form a network of high-molecular-weight complexes known as epichaperomes. In cancer, these can function as a network to enhance cellular survival, irrespective of tissue of origin or genetic background. PU-H71 targets the epichaperome to interfere with its function in diseased cells without affecting normal cells.

In myelofibrosis, the epichaperome plays a central role in optimizing the JAK-STAT pathway, allowing JAK2 to form dimers that evade inhibition with a JAK2 inhibitor such as ruxolitinib. By inhibiting epichaperome function and breaking this mechanism, PU-H71 may increase anticancer activity of JAK2 inhibitors. PU-H71 is being studied in phase 1b combination trials in myelofibrosis and advanced metastatic breast cancer.

Source: Samus Therapeutics, June 13, 2018

DRUG SAFETY ISSUES

New Fluoroquinolone Warnings

The FDA is requiring safety labeling changes for fluoroquinolone antibiotics to strengthen the warnings about the risks of mental health side effects and serious blood sugar disturbances, and to make these warnings more consistent across the labeling for all fluoroquinolones taken by mouth or given by injection.

FDA-approved fluoroquinolones include levofloxacin, ciprofloxacin, ciprofloxacin extended-release tablets, moxifloxacin, ofloxacin, gemifloxacin, and delafloxacin, with more than 60 generic versions. The new labeling changes are based on a comprehensive review of the FDA's adverse event reports and case reports published in medical literature.

Across the fluoroquinolone antibiotic class, a range of mental health side effects are described in the Warnings and Precautions section of the drug labeling, but differ by individual drug. The new class-wide labeling will require that the mental health side effects be listed separately from other central nervous system side effects and be consistent across the labeling of the fluoroquinolone class. The mental health side effects to be included are disturbances in attention, disorientation, agitation, nervousness, memory impairment, and delirium.

The recent FDA review also found instances of hypoglycemic coma where users of fluoroquinolones experienced hypoglycemia. As a result, the Blood Glucose Disturbances subsection of the labeling for all systemic fluoroquinolones will be required to explicitly reflect the potential risk of coma with hypoglycemia. The FDA also published a drug safety communication about safety information regarding hypoglycemic coma and mental health side effects with fluoroquinolones.

The FDA first added a boxed warning to fluoroquinolones in July 2008 for the increased risk of tendonitis and tendon rupture. In February 2011, the risk of worsening symptoms for those with myasthenia gravis was added to the boxed warning. In August 2013, the agency required updates to the labeling to describe the potential for irreversible peripheral neuropathy.

In 2016, the FDA enhanced warnings about the association of fluoroquinolones with disabling and potentially permanent side effects involving tendons, muscles, joints, nerves, and the central nervous system. Because the risk of these serious side effects generally outweighs the benefits for patients with acute bacterial sinusitis, acute bacterial exacerbation of

chronic bronchitis, and uncomplicated urinary tract infections, the FDA determined that fluoroquinolones should be reserved for use in patients with these conditions who have no alternative treatment options.

Source: FDA, July 10, 2018

Avoid "Maximum Powerful"

The FDA is advising consumers not to purchase or use Maximum Powerful, a product promoted for sexual enhancement that contains sildenafil, the active ingredient in Viagra. This product was identified during an examination of international mail shipments.

The FDA noted that it is unable to test and identify all products marketed as dietary supplements that have potentially harmful hidden ingredients. As a result, the agency issued a blanket warning that consumers should exercise caution before purchasing any product touted as improving sexual enhancement, helping with weight loss, or building up muscle.

FDA laboratory analysis confirmed that Maximum Powerful contains sildenafil, which may interact with nitrates found in some prescription drugs, such as nitroglycerin, and may lower blood pressure to dangerous levels. People with diabetes, high blood pressure, high cholesterol, or heart disease often take nitrates.

Source: FDA, July 9, 2018

Voluntary Recall of Drugs Containing Valsartan

N-nitrosodimethylamine (NDMA), a semi-volatile organic compound and human carcinogen, was found in several products containing the active ingredient valsartan. The FDA is issuing a voluntary recall of selected medications and says that the presence of NDMA is thought to be related to changes in the way the active substance is manufactured. A complete list is available on the FDA's website.

Source: FDA, July 13, 2018.

DEVICE APPROVALS

Valve to Treat COPD

The FDA has approved the Zephyr Endobronchial Valve (Pulmonx Inc.) to treat breathing difficulty associated with severe emphysema.

Using a flexible bronchoscope, a doctor places Zephyr valves, similar in size to pencil erasers, into the diseased areas of the lung airways during a hospital procedure. The device is intended to prevent air from entering the damaged parts of the lung and allow trapped air and fluids to escape. During inhalation, the valves close, preventing air from entering the damaged part of the lung, and during exhalation, the valves open, letting out trapped air, which is intended to relieve pressure.

The device is contraindicated for patients with active lung infections; those who are allergic to nitinol, nickel, titanium, or silicone; active smokers; and those who are not able to tolerate the bronchoscopic procedure. Patients who have had major lung procedures, heart disease, large bubbles of air trapped in the lung, or who have not responded to other treatments should talk with their providers to determine if the Zephyr valve device is appropriate for them.

The FDA reviewed the device through the premarket approval review pathway.

Source: FDA, June 29, 2018

Hemodialysis Catheter Access

The FDA has permitted marketing of two catheter-based devices designed to create a connection to veins and arteries in patients with chronic kidney disease who need hemodialysis. The FDA granted marketing authorization for the Ellipsys vascular access system (Avenu Medical) and the everlinQ endoAVF system (TVA Medical, Inc.) to make an arteriovenous (AV) fistula for patients who need hemodialysis access.

Before patients can start dialysis, an AV fistula must be created—traditionally by surgically joining an artery and a vein under the skin in the arm. After some time, the mature vein can receive the two needles used for each hemodialysis session. Surgically created AV fistulas typically take several months to heal and for the vein to mature before being usable for hemodialysis.

The devices granted marketing authorization are designed to create AV fistulas percutaneously or through the skin. A catheter is inserted into a blood vessel in the arm and is guided to the site of the planned AV fistula. The devices then deliver energy to form a connection between an upper forearm artery and an adjacent vein. The Ellipsys system uses one catheter, and the everlinQ endoAVF system uses two.

Both devices are contraindicated for creation of anastomoses in vessels that are less than 2 mm in diameter or too far apart. For both devices, complications include occlusion or stenosis of the fistula, bruising, and need for additional procedures.

Both systems were reviewed through the *de novo* premarket review pathway. Subsequent devices with the same intended use may go through the FDA's 510(k) process.

Source: FDA, June 22, 2018.

MiniMed Insulin System Use Approved in Younger Children

The FDA has expanded the approval of the MiniMed 670G hybrid closed-looped system (Medtronic)—a diabetes management device that is intended to automatically monitor glucose and provide appropriate basal insulin doses with little or no input from the user—to include patients 7 to 13 years of age with type-1 diabetes. The FDA originally approved this device in September 2017 for use in patients 14 years of age and older with type-1 diabetes.

The MiniMed 670G hybrid closed-

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looped system measures glucose levels in the body every five minutes and automatically adjusts insulin delivery by either administering or withholding insulin. The system includes a sensor that attaches to the body to measure glucose levels under the skin; an insulin pump strapped to the body; and an infusion patch connected to the pump with a catheter that delivers insulin. While the device automatically adjusts insulin levels, users must manually request insulin doses to counter carbohydrate consumption at mealtime.

The FDA evaluated data from a clinical trial of the MiniMed 670G hybrid closed-looped system that included 105 individuals 7 to 11 years of age. Study participants wore the device for approximately 3.5 months and participated in three phases of the study to evaluate both at-home and remote use. That study found no serious adverse events associated with use of the MiniMed 670G.

Risks associated with use of the system may include hypoglycemia, hyperglycemia, and skin irritation or redness around the device's infusion patch. The FDA is requiring the developer to conduct a post-marketing study to evaluate device performance in real-world settings in children between 7 and 13 years of age. This device is not approved for use in children 6 years of age or younger and in individuals who require less than 8 units of insulin per day.

Source: FDA, June 21, 2018

Eversense Glucose Monitoring

The FDA has approved the Eversense continuous glucose monitoring (CGM) system (Senseonics, Inc.) for use in people 18 years of age and older with diabetes. The system includes a fully implantable sensor to detect glucose and can be worn for up to 90 days.

Most current glucose sensors are replaced on a regular basis (generally, every seven days) to ensure that an overall CGM system is properly functioning. The Eversense CGM system uses a small sensor that is implanted just under the skin by a qualified health care provider during an outpatient procedure. After it is implanted, the sensor regularly measures glucose levels in adults with diabetes for up to 90 days.

The implanted sensor works with a novel light-based technology to measure glucose levels and send information to a mobile app to alert users if glucose levels are too high or too low. The sensor is coated with a fluorescent chemical, that when exposed to blood sugar, produces a small amount of light that is measured by the sensor. Every five minutes, measurements are sent to a compatible mobile device (e.g., smartphone or tablet) that is running a device-specific mobile app.

The FDA evaluated clinical study data from 125 individuals 18 years of age and older with diabetes and reviewed the device's effectiveness by comparing readings obtained by the Eversense CGM system to those obtained by a laboratory-based glucose analyzer. The safety of the Eversense CGM system's 90-day implantable sensor and the procedure used to implant it was also evaluated during the studies. The proportion of individuals experiencing a serious adverse event with the implanted sensor was less than 1%. The safety of this system will also be evaluated in a post-approval study.

Potential adverse effects related to the insertion, removal, and wear of the sensor include allergic reaction to adhesives; bleeding; bruising; infection; pain or discomfort; scarring or skin discoloration; sensor fracture during removal; and skin inflammation, thinning, discoloration, or redness. Other risks associated with use of the CGM system may include hypoglycemia or hyperglycemia in cases where information provided by the device is inaccurate or where alerts are missed.

Source: FDA, June 21, 2018

Wearable Opioid Addiction Treatment

The FDA has cleared a new auricular neurostimulation device (Drug Relief, DyAnsys, Inc.), to be used as an aid to reduce the symptoms of opioid withdrawal without narcotics. Providers can prescribe the device for use during opioid detoxification. The wearable device sends electrical pulses through tiny needles inserted in the ear to alleviate symptoms such as anxiety, agitation, depression, nausea, opiate cravings, and more.

The Drug Relief device is a percutaneous electrical nerve field stimulator designed to administer auricular neurostimulation treatment over 120 hours. The nonaddictive treatment allows for continuous nerve stimulation over five days. According to providers, patients may see a reduction in the symptoms of opioid withdrawal within 30 to 60 minutes of beginning treatment.

The device eases the process of detoxification, which is the first step in a comprehensive rehabilitation program. The objective is to ease symptoms while opioids are cleared from a patient's system. It can be used to help stabilize a patient during the early stages of withdrawal without side effects. Stabilization is a necessary first step before treating the patient with medication-assisted therapies.

Source: DyAnsys, Inc., June 12, 2018 ■